Comparison of NTP Diesel Exhaust and ETS Background Documents

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It seems clear that the data for ETS and the data for diesel exhaust were presented in an inconsistent manner in the respective NTP Background Documents. This lack of consistency may well explain the different classifications proposed for these two mixtures by NTP.

The purpose of this comment is to highlight significant inconsistencies in the NTP listing process for these two mixtures. In order to discuss the inconsistencies, it is necessary, obviously to refer in part to NTP's treatment of ETS. However, our discussion of NTP's decision-making with respect to ETS does not in any way express agreement with NTP's conclusions, determinations, or classification.

Results of Animal Testing Reviewed in the Two Background Documents

There are numerous similarities with respect to the data deemed by NTP to be relevant for diesel exhaust and ETS exposures regarding the possible human carcinogenicity of these two complex mixtures. NTP chose to rely on limited data for both compounds in animal testing. Based on animal data considered by NTP, diesel exhaust has been shown to be carcinogenic to the rat in a number of different laboratories, but positive results have not been consistently obtained in other animal models. Similarly, NTP selectively noted that sidestream smoke, used as a surrogate for ETS, has recently been reported by a single laboratory to statistically significantly increase the multiplicity of the spontaneous formation of lung tumors in the A/J mouse at extremely high doses. However, no statistically significant increase in the incidence of lung tumors was reported. Significantly, attempts to induce tumors in other animal models with either mainstream or sidestream smoke have repeatedly met with failure. It is quite possible that neither of these animal models is at all useful in predicting human responses for either diesel exhaust or ETS.

Epidemiological Results Reviewed in the Two Background Documents

The epidemiological results considered by NTP are similar for the two substances. A recent meta-analysis of 29 epidemiological studies investigating the possible association of diesel exhaust exposure with lung cancer (Bhatia, et al., 1998) reported a pooled relative risk of 1.33 (95% CI, 1.18-1.51). The often cited 1992 EPA risk assessment on ETS exposure (U.S. EPA, 1992) reported a pooled relative risk for 11 US studies of 1.19 (90% CI, 1.04-1.35). Given this striking similarity, it might have been anticipated that a scientific body attempting to determine the potential human carcinogenicity of the two substances would have arrived at identical classifications. However, this was not the case for the NTP. In the Board of Scientific Counselors Report on Carcinogens Subcommittee meeting of Dec. 2-3, it was recommended that ETS be classified as a "known human carcinogen," whereas the recommendation was that diesel exhaust particulates be classified as "reasonably anticipated to be a human carcinogen." Is it possible that different conclusions were reached by the NTP subcommittee based upon differences in the manner in which the two respective background documents presented the data? This analysis will explore this possibility.

PM3006569636

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Although the respective background documents provide considerable data on chemical composition of diesel exhaust and ETS, as well as animal testing data, it is clear that the NTP subcommittee relied almost exclusively on the reported epidemiological data in forming its opinion. Therefore, this comparison will be restricted to Section 3, Human Studies, for both background documents. Both documents are organized in the same manner. The first part is devoted to key summary analyses of the epidemiology, the second part to "current epidemiology studies," and the third part is a concluding discussion. Despite this similarity in organization, however, there are major differences between the two documents.

Section 3 of the ETS background document cites three summary reports; namely, IARC (1986), U.S. EPA (1992), and California EPA (CalEPA) (1997). The background document on diesel exhaust, however, cites a single report; namely, IARC (1989). Risk assessments have been prepared by both EPA and CalEPA on diesel exhaust as well; however, no reference was made to these two reports in the background document on diesel exhaust. NTP might argue that perhaps there is good reason for not referencing the EPA risk assessment on diesel exhaust, since it has never officially been issued. However, the lack of reference to the CalEPA risk assessment is difficult to understand. For example, in June 1998 the CalEPA Air Resources Board (California Environmental Protection Agency, 1998) identified diesel exhaust as a toxic air contaminant. The Air Resources Board proposed amending Titles 17 and 26 of the California Code of Regulations, Section 93000, to include diesel exhaust as a toxic air contaminant and recommended that no threshold limit can be established below which adverse health effects are not anticipated. This recommendation was based in part on the epidemiological studies published on diesel exhaust:

> The lung cancer findings are consistent and the association is unlikely to be due to chance. These epidemiological studies strongly suggest a causal relationship between occupational diesel exhaust exposure and lung cancer. (Appendix II, p. 4)

Given this relevant finding by the California EPA with respect to diesel exhaust, it is difficult to understand why this information was not included in NTP's background document.

A second major difference between the two documents is the manner in which recent epidemiological studies were summarized. For the diesel exhaust background document fourteen "recent" (six cohort and eight case-control) epidemiological studies were discussed, "recent" being defined as being published after the 1989 IARC report. Each discussion concluded with a brief summary of the strengths and weaknesses of the study. In almost every case, the background document pointed out that the study was limited by its lack of actual exposure data. Four of the case-control studies did provide at least a semi-quantitative measure of exposure, and three of these four studies reported statistically significant OR's at the highest level of exposure. Gustavsson, et al. (1990) reported an OR of 2.43 (95% CI, 1.32-4.47) for 10 cases at the highest level of exposure; Steenland, et al. (1998) reported an OR of 1.64 (95% CI, 1.09-2.49) for the highest quartile of exposure; while Swanson, et al. (1993) reported an OR of 2.5 (95% CI, 1.40-4.4) for drivers of heavy trucks for more than 20 years (121 cases). The NTP background document on diesel exhaust mentioned other weaknesses as well: lack of adjustment for possible confounding (a point raised for almost all of the studies) and the small number of cases on which certain studies based their risk estimates.

PM3006569637

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In contrast, the ETS background document discusses only four "recent" epidemiological studies, "recent" being defined as being published after the 1986 IARC report – one cohort study and three case-control studies. There is no suggestion that weaknesses, for example, lack of adjustment for confounding, are present in any of these studies. This is despite the fact that none of these studies actually measured ETS exposure, and that only two of the four adjusted in any way for confounding. We have described many of these weaknesses in some detail in our critique of the Draft Background Document for ETS, included in this submission.

Another major difference between the two documents is related to the conclusions. The diesel exhaust background document concludes with the following paragraph:

> In summary, DE exposure is associated with lung cancer in the majority of studies, with a (sic) overall relative risk of about 1.3. Some studies found dose-responses, with higher risks in the more heavily exposed groups. Although the risk is small, it is not readily explained by confounding by smoking or asbestos exposure. Most studies had little or no quantitative information on actual exposures, but the resulting misclassification would be more likely to disguise an effect than to produce a spurious one and may provide an explanation for the small size of the risk. (p. 35)

The ETS background document, on the other hand, concludes as follows:

> In summary, it appears unlikely that either confounding or other types of bias can account for the risk ascribed to ETS exposure. The consistency of risks observed across individual studies conducted with various populations and methodologies, the presence of an exposure-relationship in many studies, and the biological plausibility of the relationship all argue strongly that the association of ETS exposure with lung cancer is causal.

The major difference between these two conclusions is that the ETS background document clearly adopts the conclusion that the association between ETS exposure and lung cancer is causal, but the diesel exhaust background document fails to reach that conclusion. According to NTP, epidemiological studies for both substances show an apparent weak association – 1.3 for diesel exhaust and 1.19 for ETS (U.S. EPA, 1992). Further, according to NTP, epidemiological studies for both substances reported dose-response relationships. Under NTP's analysis, results for both substances were equally consistent – or inconsistent depending on how one views the data. Lastly, there is no NTP argument from the perspective of biological plausibility which accounts for the difference in classification between ETS and diesel exhaust.

Discussion at the December 2 - 3 Meeting

With some striking inconsistencies regarding the manner in which NTP reviewed the epidemiology of diesel exhaust and ETS having been identified, the question remains: is there any indication that these differences in any way influenced the decisions that NTP reached regarding these two substances? An examination of the transcript of the NTP Dec. 3 discussion of diesel exhaust makes

PM3006569638

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it clear that this may indeed have been the case. Two quotations illustrate this point. The first is by Dr. Belinsky:

> Just a comment again to comment on the epi data with diesel versus ETS: I mean, the confidence intervals on a lot of these epi diesel studies were very large, going down to .7 and extending. And with the ETS they were much, much tighter.

This comment is a reflection of the fact that NTP provided data for 14 studies on diesel exhaust and only four studies for ETS. Had 14 "recent" ETS studies been discussed, equally wide confidence intervals would have been observed. The second comment is by Dr. Frederick:

> Cogent to the question, I am not at all convinced that we do a good job of controlling for smoking in a group like truck drivers, because I have to think that long hours in a cab in tightly controlled conditions, I am not entirely convinced that we have got ways of sorting out the effect of these things. And it is at least, you know, casual experience, a group that does an awful lot of smoking.

Dr. Frederick's comments refer, of course, to the possibility that active smoking could have confounded the reported association between diesel exhaust exposure and lung cancer. Certainly NTP viewed this as a potential concern, and consequently the NTP document carefully pointed out that many of the studies had not corrected the reported odds ratios or relative risks for smoking. This is despite the fact, however, that the conclusions stated that, "[A]lthough the risk is small, it is not readily explained by confounding by smoking or asbestos exposure." The ETS background document, on the other hand, bases its conclusion that confounding has been adequately corrected for in the epidemiology of ETS and lung cancer on a single study (Fontham, et al., 1994). This is despite the fact that a careful analysis of all of the data suggests that confounding can account for some part, although probably not all, of the risk.

In conclusion there seems to be clear evidence that the data for ETS and diesel exhaust were not presented at all consistently by their respective background documents, and that this lack of consistency may well explain the different classifications given to these two mixtures.

REFERENCES

1. Bhatia, R., P. Lopipero, and A. H. Smith. 1998. Diesel exhaust and lung cancer. *Epidemiology*. 9:84-91.

2. California Environmental Protection Agency. 1998. "Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant," Air Resources Board, June 1998.

3. California Environmental Protection Agency. 1997. Health Effects of Exposure to Environmental Tobacco Smoke. Cal EPA office of environmental health hazard assessment.

PM3006569639

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4. Fontham, E. T., P. Correa, P. Reynolds, A. Wu-Williams, P. A. Buffler, R. S. Greenberg, V. W. Chen, T. Alterman, P. Boyd, and D. F. Austin. 1994. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study [published erratum appears in *JAMA* 1994 Nov 23 - 30; 272(20):1578]. [see comments]. *JAMA* 271:1752-1759.

5. Gustavsson, P., N. Plato, E. B. Lidstrom, and C. Hogstedt. 1990. Lung cancer and exposure to diesel exhaust among bus garage workers. *Scand.J.Environ.Health* 16:348-354.

6. IARC (International Agency for Research on Cancer). 1986. Evaluation of the carcinogenic risk of chemicals to humans—Tobacco smoking. IARC Monograph 38.

7. IARC (International Agency for Research on Cancer). 1989. IARC monographs on the evaluation of carcinogenic risk to humans. Diesel and gasoline engine exhausts and some nitroarenes. 46:1-458.

8. Steenland, K., J. Deddens, and L. Stayner. 1998. Diesel exhaust and lung cancer in the trucking industry: exposure-response analyses and risk assessment. *Am.J.Ind.Med.* 34:220-228.

9. Swanson, G. M., C. S. Lin, and P. B. Burns. 1993. Diversity in the association between occupation and lung cancer among black and white men. *Cancer Epidemiol.Biomarkers.Prev.* 2:313-320.

10. U.S EPA. 1992. Environmental Protection Agency. Respiratory health effects of passive smoking: lung cancer and other disorders. EPA Office of Research and Development, Washington, D. C. EPA/600/6-90/006F

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Source: https://www.industrydocuments.ucsf.edu/docs/lsdj0001